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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.     | CONFIRMATION NO.       |
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| 10/529,749  | 03/30/2005  | Shunichi Kuroda      | GRT/1035-579            | 1581                   |
| 23117 7590 09/07/2007<br>NIXON & VANDERHYE, PC<br>901 NORTH GLEBE ROAD, 11TH FLOOR<br>ARLINGTON, VA 22203 |             |                      | EXAMINER<br>PENG, BO    |                        |
|   |             |                      | ART UNIT<br>1648        | PAPER NUMBER           |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/529,749

Applicant(s)

KURODA ET AL.

Examiner

Bo Peng

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 June 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☒ Claim(s) 1 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/30/05&amp;4/25/05</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Applicant's election of Group I, Claims 1-9, filed on June 19, 2007, is acknowledged. Applicant also elected species: HBsAg whose hepatocyte recognition site is modified to bFGF. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The requirement is made FINAL.
2. Accordingly Claims 1-10 are pending. Claim 10 is withdrawn as non-elected. Claims 1-9 are considered in this Office action.

### ***Information Disclosure Statement***

3. The information disclosure statements submitted on March 30, 2005, and April 25, 2005, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. The initialed and dated copies of the Applicant's IDS form 1449 are attached to the instant Office action.

### ***Drawings***

4. The following informalities have been noted: Neither the specification nor Figures indicates to what the drawings and the labels "1, 2, 3 and 4" in Figures 1, 2, and 15 refer. Applicant is required to amend the Brief Description of the Drawings in Applicant's disclosure to indicate what the drawings represent.
5. Figure 4 is not consistent with the specification Para [0102] because it lacks the key component of HBcAg. Figure 14 lacks labels. It is not clear what are the bands in the figure.

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Formal drawings are required in response to the instant Office action.

***Claim Objection***

6. Claim 1 is objected to because of a lack of clarity. Claim 1 recites: "Hollow nanoparticles that comprise particle-forming first proteins, containing a bio-recognizing molecule for recognizing a specific cell, wherein at least one of the first proteins interacts with a second protein forming a capsid structure". Since plural form "hollow nanoparticles" contains a group of different nanoparticles that comprise different "particle-forming first proteins", it is not clear how only one of different "particle-forming first proteins of different nanoparticles interacts with a second protein ...".

***Claim Rejections - 35 USC § 112, first paragraph***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'"

Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997);

In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen

Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re

Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d

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731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

8. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. Claims 1-9 are directed to hollow nanoparticles that comprise particle-forming first proteins, containing a bio-recognizing molecule for recognizing a specific cell, wherein at least one of the first proteins interacts with a second protein forming a capsid structure, wherein the first protein comprises a hepatitis B virus surface-antigen protein, wherein the first protein comprises a hepatitis B virus surface-antigen protein whose hepatocyte recognition site is modified to another bio-recognizing molecule, wherein the first protein comprises a hepatitis B virus surface-antigen protein whose hepatocyte recognition site is modified to a beta-cellulin or a basic fibroblast growth factor, wherein the second protein comprises a hepatitis B virus core-antigen protein, wherein the hollow nanoparticles are formed by transferring a gene encoding the

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first protein and a gene encoding the second protein to a single eukaryotic cell by separate vectors, so that the respective genes are co-expressed in the eukaryotic cell, wherein the eukaryotic cell is a yeast cell, wherein the gene encoding the second protein is transferred by a vector having an Aureobasidin A-sensitive gene. Claim 9 is directed to a drug that is made of the hollow nanoparticles as set form in Claim 1, wherein a target cell substance is encapsulated in the hollow nanoparticles.

10. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

11. *Nature of the invention.* The invention is drawn to a hollow nanoparticle that comprises two particle-forming proteins, wherein the first protein is HBsAg, in which HBsAg is manipulated to incorporate a basic fibroblast growth factor (bFGF), wherein the second protein comprises a HBcAg.

12. *Breadth of the claims.* The claims are extremely broad, encompassing any possible nanoparticles that contains two or more particle-forming proteins in which an uncharacterized target cell substance is encapsulated and a foreign molecule is displayed on the first protein.

13. *State of the prior art and predictability of the art.* At the time the invention was made, some viral like particles (VLP) have been successfully made, such as HBsAg, HBcAg, HPV 16 L1, HPV 18 L1, SIV etc. Construction of VLPs containing two particle-forming proteins was also reported, such as VLP of HBsAg/HBcAg (Shiosaki 1991). However, the prior art teaches specific sequences and structures are required for a protein to form a stable VLP. For example, Shiosaki (1991) teaches that co-expression of four structural genes of HBV encoding three envelope proteins (HBsAg S, M, L) and HBcAg can lead to the production of nanoparticles in a yeast cell (Entire document, particularly see Summary, pp 145-148, and Figures 2-5). Shiosaki

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shows that elimination of one of these four components abolished the ability to form HBsAg-HBcAg particles.

14. The prior art also teaches there are restrictions on the inserted sequences and their sizes when foreign sequences are incorporated into VLPs. Usually, only small peptides are successfully displayed on VLPs. For example, Ward *et al* (Virus Genes, Vol. 23: p. 97-104, 2001) tried to package the hepatitis C virus (HCV) core protein into HBsAg particles. Ward *et al* found that only limited chimeric proteins were packaged into viral particles, due to poor expression and the size limit to the insert (see in particular the abstract and Fig. 3). Thus, the prior art teaches that it is unpredictable to assemble a foreign protein or substance into a viral particle.

15. *Working examples and Guidance in the specification.* In *re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the specification provides some working examples showing how to construct chimeric protein HBsAg L-bFGF, and co-expression of HBsAg L-bFGF and HBcAg in yeast cells (Example 1-3). However, the specification does not show how the alleged nanoparticles that comprise two particle-forming proteins are formed after co-expressing HBsAg L-bFGF and HBcAg in yeast cells. Specifically, the specification shows that major fraction of particles produced is HBsAg L-bFGF with estimated density of about 1.20 g/ml (shown as Fraction 3 in Figure 12b), which does not encapsulate the second particle-forming protein HBcAg with estimated density of about 1.25 g/ml (Para [0103] and [0115]). No data shows that HBcAg is actually forming a capsid structure. Moreover, Figure 15 shows that the obtained particles with density of about 1.25 g/ml

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appears to have the second particle forming protein HBcAg externally interact with HBsAg L protein (Para [0119]). However, the specification does not disclose what is the advantage to have the second protein HBcAg, which naturally form a capsid structure insides HBsAg, is somehow attached to HBsAg externally instead. It is not clear whether or not a unified nanoparticle containing HBsAg L-bFGF-HBcAg is formed.

16. Moreover, the specification provides little guidance regarding how to make and use a broad range of nanoparticles, nor show how to encapsulate “a target cell substance” in hollow nanoparticles, nor their applications as a drug for treating any diseases. There is little guidance provided in the specification what are the structural requirements for encapsulating “a target cell substance” into uncharacterized nanoparticles.

17. *Amount of experimentation necessary.* It would require extensive research to make and use alleged hollow nanoparticles. In order for the full breadth of the invention to be enabled, one skilled in the art would have to do an **undue** amount of experimentation to make and test all particle-forming proteins to see if they can encapsulate any substance, and test them to see if they can be “a drug” for treating any diseases.

18. For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed nanoparticles.

### ***Claim Rejections - 35 USC § 102***

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1, 2, 5-8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Shiosaki (1991; Gene 106:143-149, cited in IDS).

21. Claims 1, 2, 5-8 and 9 are directed to hollow nanoparticles that comprise particle-forming first proteins, containing a bio-recognizing molecule for recognizing a specific cell, wherein at least one of the first proteins interacts with a second protein forming a capsid structure, wherein the first protein comprises a hepatitis B virus surface-antigen protein, wherein the second protein comprises a hepatitis B virus core-antigen protein, wherein the hollow nanoparticles are formed by transferring a gene encoding the first protein and a gene encoding the second protein to a single eukaryotic cell by separate vectors, so that the respective genes are co-expressed in the eukaryotic cell, wherein the eukaryotic cell is a yeast cell, wherein the gene encoding the second protein is transferred by a vector having an Aureobasidin A-sensitive gene.

22. Shiosaki teaches that a hollow nanoparticle with a diameter of about 40 nm and a density of 1.25 g/ml that comprises HBsAg protein and HBcAg protein (Entire document, particularly see Summary, pp 145-148, and Figures 2-5). Shiosaki teaches that the nanoparticle is produced by co-expressing all four genes encoding the major S, middle S and large S and the core protein in a yeast cell. Shiosaki teaches that such a particle is useful for vaccine development.

23. Since Shiosaki's particle is DNA-less with a diameter of about 40 nm, and contains first particle-forming protein HBsAg that has a bio-recognizing molecule for recognizing hepatocytes, and a second particle-forming protein HBcAg, Shiosaki's particle meets the structural limitations in the claims. Thus, the instant Claims 2, 5-8 and 9 are anticipated by

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Shiosaki.

***Remarks***

24. No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

BP  
Bo Peng, Ph.D.  
August 31, 2007



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